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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,578	05/03/2002	Audrey Goddard	P3230R1C001-168	2392

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,578	GODDARD ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 1/27/06 has been entered in full. Applicants have amended the specification.

Applicants have not made any amendments to the claims. Applicants query as to whether the amendment submitted after final was entered into the case (to insert the word "isolated" before the word "antibody" in claim 1). The Examiner notes here that the amendment was considered to have been entered at the time of mailing of the 10/27/2005 Office Action, and regrets that this was not explicitly noted in the action. Therefore, the claim set that Applicants have presented 1/27/06 correctly represents the claims 1-5 under consideration in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Information Disclosure Statement

The Information Disclosure Statement of 1/27/2006 has been considered.

Specification

The objections to the specification are *withdrawn* in view of Applicants' amendments to the specification, noted by Applicants on page 5 of the 1/27/06 response.

Claim Rejections - 35 USC § 101, utility

Claims 1-5 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Upon further consideration of Applicants' arguments and the data provided in the specification in Example 18, the Examiner withdraws the portion of the utility rejection that is based on whether or not PRO1158 mRNA can be used as a diagnostic (pg 3-5 of the 10/27/05 Office Action). However, the portion of the utility rejection based on whether or not PRO1158 protein can be used as a diagnostic is maintained for the reasons of record (pg 5-8 of the 10/27/05 Office Action). The Examiner maintains that mRNA levels are not necessarily predictive of protein levels, and that changes in mRNA levels are not necessarily predictive of changes in protein levels. Applicants' arguments as they pertain to this portion of the rejection (1/27/2006; pg 14-41) have been fully considered but are not deemed to be persuasive for the following reasons.

The Examiner previously argued that, "in organisms ranging from yeast to human, changes in mRNA levels are not predictive of changes in encoded polypeptide levels, especially in cancerous cells". The following references were cited in support of this argument: Hu (2001); LaBaer (2003); Haynes (1998); Gygi (1999); Chen (2002); Lichtinghagen (2002) and Fessler (2002).

In response to the Examiner's argument, Applicants summarize their argument as such: "it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1158 polypeptide in lung tumor, it is likely that the PRO1158 polypeptide is likewise differentially expressed in lung tumor; and antibodies to protein differentially expressed in certain tumors have utility as diagnostic tools" (pg 14; emphasis by Applicants). Applicants argue at pgs 15-27 that the references cited in the 10/27/05 rejection are "either irrelevant, not contrary to Applicants' arguments or actually offer support for Applicants' position" (pg 15). These references include Hu (2001); LaBaer (2003); Haynes (1998); Gygi (1999); Chen (2002); Lichtinghagen (2002) and Fessler (2002). In support of their argument, Applicants further turn to support from previously submitted declaration and references (pg 28-31) and from newly submitted references (pg 31-36).

Applicants' arguments have been fully considered but are not found to be persuasive. Applicants' arguments regarding the references of Hu, LaBaer, Haynes,

Gygi, Chen, Lichtinghagen and Fessler have been fully considered. The previously and newly cited references submitted by Applicants in support of their argument have been fully considered. It is clear that the correlation between protein and mRNA levels is an active area of investigation and different studies have reported conflicting results. However, given full consideration of the previously submitted references, newly submitted references, and the relevant art, the Examiner does not find Applicants' arguments to be persuasive. Each argument will be addressed in turn.

With regard to the references of Hu and LaBaer, the Examiner finds Applicants' arguments persuasive (pg 15-17). These references are not relevant to the Examiner's argument because they are directed to the nexus between gene expression and a role in cancer, rather than to gene or protein expression as a diagnostic, and do not discuss the correlation between mRNA and protein expression.

With regard to the references of Haynes, Gygi, and Chen, Applicants argue that these studies only provide teachings regarding the predictability of the correspondence of steady-state mRNA and protein levels, and do not speak to whether or not a detectable change in mRNA level will lead to a detectable change in protein level, and therefore are not relevant to Applicants' argument (pg 17-22). The Examiner finds these arguments persuasive. The Examiner agrees with Applicant that these references do not provide teaching as to whether changes in mRNA expression are generally reflected as changes in protein expression.

Applicants further contend that the limited teachings in Chen that do address changes in mRNA level support corresponding changes in the level of encoded protein (pg 20). Specifically, Applicants argue that Figures 2A-2C show a correlation between mRNA/protein pairs for three specific genes, and that this supports Applicants' assertion of a correlation between mRNA and protein changes.

Applicant's arguments have been fully considered but are not found to be persuasive. The results in Chen shown in Figure 2A-2C represent three examples wherein protein levels were correlated with mRNA (out of 17 identified). Chen found 137 protein spots wherein protein levels were not correlated with mRNA levels. However, Chen does not report the individual variation within any of these samples (which

included normal tissue and tumor tissue). Therefore, these samples may or may not have included mRNA and/or protein levels that were differentially expressed. Chen simply does not provide enough information to address the issue whether changes in mRNA levels generally result in similar changes in protein levels. All that Chen clearly teaches is that mRNA levels do not predict protein levels, as they disclose at pg 304 that "[t]he use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of a protein present in a given cell or tissue" (see pg 304, right column).

Applicants also contend that the relevant art does teach a correlation between mRNA and encoded protein levels; in support of this argument Applicants submit Exhibits 14-21, containing a total of 33 references (pg 35-36).

Applicants' arguments have been fully considered but are not found persuasive. With the exception of Exhibit 14 (Futcher), Exhibits 14-21 are all directed to analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. A more comprehensive analysis like Haynes (80 proteins examined), Gygi (150 proteins examined), Chen (164 proteins examined) or Futcher (148 identified proteins) more accurately describes general trends. The Examiner agrees with Applicants that Futcher is a study similar to Gygi but reaches different conclusions that Gygi. However, Futcher also teaches, "the correlation is far from perfect, there is at least a 10-fold range of protein abundance" (pg 7360) and "Despite generating broadly similar data, Gygi et al reached markedly different conclusions...Gygi et al feel that mRNA abundance is a poor predictor of protein abundance...These different conclusions are partly a matter of viewpoint. Gygi focuses on the fact that the correlations of mRNA and codon bias with protein abundance are far from perfect, while we focus on the fact that, considering the wide range of mRNA and protein abundance and the undoubted presence of other mechanisms affecting protein abundance, the correlations are good" (pg 7367 of Futcher, 1999. Molecular and Cellular Biology. 19(11): 7357-7368; Applicants only submitted the abstract of Futcher;

the Examiner has placed the entire Futcher reference on the PTO-892 attached to this Office Action). For these reasons, the Examiner maintains that these references demonstrate the mRNA levels do not necessarily correspond to protein levels, although as noted above the Examiner acknowledges that these references do not address whether observable changes in mRNA levels will be reflected as observable changes in protein levels.

With respect to Lichtinhagen, Applicants' arguments are found persuasive that the reference also does not address changes in mRNA levels, because the mRNAs studied by Lichtinhagen show either no change or little change (33%) in expression between normal and differential expression. It is noted that Applicants' argument with respect to Sterns and Wang reference (Exhibit 2) are addressed below.

With regard to the Lian and Fessler references, Applicants argue that although the authors characterize the mRNA and protein levels as showing a poor correlation, this does not reflect a lack of correlation between a change in mRNA level and a corresponding change in protein level. Applicants argue (pg 25) that of the 28 differentially expressed proteins identified by Lian, only one that is differentially expressed at the mRNA shows a corresponding change in protein level (pg 25 of Applicants' response). Applicants further argue (pg 25-26) that Fessler identifies 6 differentially regulated proteins that also show a change in mRNA expression, of which 5 show a similar change, and that this actually supports Applicants' argument.

These arguments have been fully considered but are not found persuasive. In contrast to Applicants' arguments, the Examiner considers the results in Lian and Fessler to support the position that changes in mRNA do not necessarily reflect changes in protein level. Applicants' arguments focus on the proteins that were noted to have a change in protein expression. However, in both studies, the researchers found a large number of transcripts that were differentially expressed than proteins that were differentially expressed. Lian characterized 837 transcripts that changed substantially during MPRO (promyelocytic cell) differentiation (pg 515). In view of the 837 transcripts that were differentially expressed, it is significant that only one of 28 identified proteins (out of 50 that were noted to be differentially expressed) showed a corresponding

change in mRNA. If, as Applicants argue, that changes in mRNA generally lead to changes in protein level, one would expect many more of the 837 differentially expressed transcripts to be identified as a differentially expressed protein. Similarly, Fessler identified 100 genes that were upregulated in human neutrophils exposed to bacterial lipopolysaccharide (LPS) (pg 31293 and Table I), but only identified 8 proteins that were upregulated to a statistically significant degree (pg 31393 and Table III).

Applicants refer to previously submitted declarations and references in support of their arguments Applicants that changes in the level of mRNA correspond to changes in the level of the encoded protein (pg 28-31). The Declarations of Grimaldi (second declaration) and Polakis discuss the likelihood that if the nucleic acid is differentially expressed in tumors, then the encoded polypeptide will also be. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. Applicants also assert that the references of Alberts, Lewin, Zhigang and Meric support the statements of Grimaldi and Polakis.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. While the Examiner agrees with the teachings of Alberts and Lewin that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts (Exhibit 1) also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Exhibit 2 at pg 453). Furthermore, while Zhigang provides an example of a high degree of correlation between protein and mRNA expression of a specific antigen, more comprehensive studies (Lian and Fessler, cited above; Nagaraja (2006), Waghray (2001), and Sagynaliev (2005), cited below) show a different general trend. Applicants also have submitted Meric et al., 2002, which states the following:

> The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying

differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription.

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974).

In addition to the previously submitted references, Applicants submit 81 new references (Exhibits 2-13) in support of their argument (pg 31-35). These references have been fully considered by the Examiner but are not found to be persuasive. First of all, except for the Orntoft reference (cited at pg 31), each of the references submitted by Applicants is directed to a single gene, or a small number of genes. These references are consistent with Chen who found 17% of proteins do show correlation between mRNA and protein, and the examples of these proteins in Chen that show that changes in mRNA correlate with changes in protein level. However, these studies examining the expression of small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined, specifically, Nagaraja (2006), Waghray (2001) and Sagynaliev (2006) which are described below.

With regard to the Orntoft reference, Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one.

Applicants' arguments with respect to Orntoft have been fully considered but are not found to be persuasive. Orntoft compared the mRNA and proteins levels of about 40 well-resolved and focused abundant proteins with known chromosomal locations (see pg 42). The instant specification does not teach whether or not PRO1158 is a "well focused abundant" protein with a known chromosomal location as characterized by Orntoft. Furthermore, other relevant publications (Nagaraja (2006), Waghray (2001),

and Sagynaliev (2005)) report that increases in mRNA and protein samples are not correlated (see below).

The Examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a changes in the mRNA level. Comprehensive studies comparing changes in expression of the transcriptome and proteome support this argument. Nagaraja (2006) teaches, "We have characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231)...the proteomic profiles indicated altered abundance of few proteins as compared to transcript profiles" (See abstract of Nagaraja, 2006, Oncogene. 25: 2328-2338).

Nagaraja further teaches, "The comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*" (pg 2329) and "As dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (pg 2335). Similarly, Waghray (2001) teaches, "we have analyzed gene expression changes induced by dihydrotestosterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels" (see Abstract of Waghray, 2001. Proteomics. 1: 1327-1338). Waghray identified transcripts from 16570 genes and found "351 genes were significantly altered by DHT treatment at the RNA level." Waghray identified 1031 protein and found 44 protein spots that changed in intensity (either increased or decreased). Twenty-nine of these proteins were identified and "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level (Table 4)" If changes in protein generally reflected mRNA changes, based on the fact that 2% of the genes analyzed had a change in transcript levels (351 out of 16570 genes), one would expect at least 2% of protein levels to change, or 22 out of 1031 protein spots. Therefore, it is significant that while Applicants found 44 proteins that did change, very few of the identified ones had a similar change in mRNA expression.

In a review of gene expression in colorectal cancer (CRC), Sagynaliev (2006) teaches, "One thousand two-hundred and forty genes have been reported to be dysregulated (up- and/or down-regulated) in human CRC, representing about 5% of the 20000-25000 human genes" (pg 3067). Sagynaliev also teaches, "a total of 408 proteins were found to be differentially expressed in human CRC in at least one study" and importantly, "It is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (pg 3068).

In summary, it is clear that Nagaraja, Waghray and Sagynaliev support that changes in mRNA expression frequently does not result in changes in protein expression. Therefore, the Examiner maintains that Applicants' measurement of an increase of PRO1158 mRNA does not provide a specific and substantial utility for the encoded protein, or an antibody to the protein.

Claim Rejections - 35 USC § 112, 1st paragraph

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Applicants' arguments (1/26/06; pg 40-41) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants submit that as the claimed invention is supported by a specific and substantial asserted utility, one of skill in the art would know how to use the claimed invention without undue experimentation.

Applicants' arguments have been fully considered but are not found persuasive. For the reasons described above in the section "Claim Rejections – 35 USC § 101", the

claimed invention is not supported by a specific and substantial asserted utility, and therefore it is maintained that one of skill would not know how to use the claimed invention without undue experimentation.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JANET L. ANDRES
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